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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/989,974	11/20/2001	Emi Nunokawa	251002009300	1713
25225	7590	12/03/2003	EXAMINER	
MORRISON & FOERSTER LLP 3811 VALLEY CENTRE DRIVE SUITE 500 SAN DIEGO, CA 92130-2332				MOHAMED, ABDEL A
ART UNIT		PAPER NUMBER		
		1653		

DATE MAILED: 12/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	09/989,974	NUNOKAWA ET AL.	
	<b>Examiner</b>	<b>Art Unit</b>	
	Abdel A. Mohamed	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

1)  Responsive to communication(s) filed on 24 June 2003.

2a)  This action is **FINAL**.                            2b)  This action is non-final.

3)  Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## **Disposition of Claims**

4)  Claim(s) 1-17 is/are pending in the application.  
4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.  
5)  Claim(s) \_\_\_\_\_ is/are allowed.  
6)  Claim(s) 1-17 is/are rejected.  
7)  Claim(s) \_\_\_\_\_ is/are objected to.  
8)  Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

9)  The specification is objected to by the Examiner.

10)  The drawing(s) filed on \_\_\_\_\_ is/are: a)  accepted or b)  objected to by the Examiner.

    Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

    Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)  The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. §§ 119 and 120**

12)  Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a)  All b)  Some \* c)  None of:  
1.  Certified copies of the priority documents have been received.  
2.  Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
3.  Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).  
\* See the attached detailed Office action for a list of the certified copies not received.

13)  Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet, 37 CFR 1.78.  
a)  The translation of the foreign language provisional application has been received.

14)  Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet, 37 CFR 1.78.

**Attachment(s)**

1)  Notice of References Cited (PTO-892) 4)  Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_ .  
2)  Notice of Draftsperson's Patent Drawing Review (PTO-948) 5)  Notice of Informal Patent Application (PTO-152)  
3)  Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5. 6)  Other: \_\_\_\_\_

**DETAILED ACTION**

**ACKNOWLEDGMENT FOR PRIORITY, IDS, STATUS OF THE APPLICATION AND CLAIMS**

1. The communication for claiming priority and the information disclosure statement (IDS) and Form PTO-1449 filed 3/28/02 and 6/24/02, respectively are acknowledged, entered and considered. Acknowledgement is made of Applicant's claim for priority based on Japanese Application Number 2001-065799, having filing date of 3/8/01. Receipt is acknowledged of papers submitted under 35 U.S.C. § 119, which papers have been placed of record in the file. Claims 1-17 are present for examination.

**CLAIMS REJECTION-35 U.S.C. § 112 <sup>2nd</sup> PARAGRAPH**

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:  
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 3, 4, 6, 7, 11 and 12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 3 is indefinite in the recitation "*Escherichia coli*". The comma (,) after coli should be removed. It is believed to be typographical error (See e.g., claim 4). Appropriate correction is required.

Claim 6 is indefinite in the recitation "10,000 to 100,000". It is not clear the molecular weight recited is in Dalton or Kilo Dalton. Amendment of the claim to recite "10,000 Da to 100,000 Da" as disclosed on page 4, lines 9 to 10 in the instant specification is suggested.

Claim 7 is indefinite in the recitation the acronym "ATP". Use of the full terminology at least in the first occurrence would obviate this rejection.

#### **CLAIMS REJECTION-35 U.S.C. § 103(a)**

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Spirin et al. (Science, Vol. 242, pp. 1162-1164, 25 November 1998) taken with Hendrickson (Science, Vol. 254, pp. 51-58, 4 October 1991) and Japanese Patent No. A-2000-17569.

The reference of Spirin et al. teaches similarly as the instantly claimed invention method of synthesizing a protein using a cell-free protein synthesis system comprising a cell extract, a nucleic acid coding for said protein, and amino acids for the substrate of said protein. The reference further discloses a creatine phosphokinase as an ATP regenerating system and the use of cell extract of prokaryotic (*Escherichia coli*) and euokaryotic for synthesizing polypeptides. Thus, the reference clearly discloses the cell-free protein synthesis system which is *in vitro* protein synthesis system using a cell extract, euokaryotic or prokaryotic (e.g. *E. coli*) cell extract containing factors required for protein synthesis such as RNA (See e.g., pages 1162-1163 and Figures 1 and 3) as directed to claims 1-3, 5 and 7.

The reference of Spirin et al. differs from claims 1-17 in not teaching a method for producing a protein suitable for X-ray crystallographic analysis by using an amino acid comprising a heavy atom such as selenomethionine or selenosysteine and a protein synthesis system using a dialysis method. Although, the primary reference of Spirin et al. suggests by stating that the methods may be modified for their biochemical and physical studies and the possibilities of protein engineering can be also significantly extended, and as such, new development in biotechnology based on preparative cell-free translation system continuous action is anticipated. However, the secondary reference of Hendrickson teaches the application of wavelength anomalous diffraction (MAD) in a number of structure determinations for any kind of heavy atom in the protein e.g., containing selenomethionine, wherein the effect can be exploited in X-ray

crystallographic studies in biological macromolecules by making diffraction measurements at selected wavelength associated with a particular resonant transition (See e.g., pages 51, 53, 58 and Table 1) as directed to claims 1 and 8-14. Thus, in view of the primary reference's method which harmonizes the biological method with the chemical method, and fully utilizes excellent features of organisms, developments of cell-free protein synthesis system to produce *in vitro* by using a cell extract, one of ordinary skill in the art would have been motivated to adapt the teachings of the secondary reference into the primary reference for the intended purpose of obtaining a method for producing a protein suitable for X-ray crystallographic analysis by synthesizing a protein using a cell-free protein. Further, the reference of Japanese Patent No. 2000-175695 teaches a synthesis system using dialysis, which resulted in enabling the mass transfer of the inner liquid, and the outer liquid to recover the polypeptide (See abstract) as directed to claim 2. Therefore the combined teachings of the prior art teach a method for producing a protein suitable for X-ray crystallographic analysis, by synthesizing a protein using a cell-free protein system comprising a cell extract, a nucleic acid coding for said protein, and amino acids for the substrate of said protein, wherein said amino acid comprises at least one amino acid comprising a heavy atom.

In regard to the introduction rates of amino acids comprising a heavy atom to the protein, the rate can be analyzed by generally known methods such as mass spectrometry and/or amino acid composition analysis as acknowledged on page 9, lines 3-5 in the instant specification. Thus, it is within the purview of ordinary skill in the art to which this invention pertains to adjust the heavy atom in relation to the amino acid based on the objective of desired.

With respect to claims 15-17, the claims are in product-by-process format, and as such, it is the novelty and patentability of the instantly claimed product that need be established and not the recited process steps, *In re Brown*, 173 USPQ 685 (CCPA 1972); *In re Wertheim*, 191 USPQ (CCPA 1976). Further, the prior art described the product as old, *In re Best*, 195 USPQ 430, 433 (CCPA 1977); (See MPEP 706.03 [e]). Hence, the burden of proving that the process limitation makes a different product is shifted to Applicants. *In re Fitzgerald*, 205 USPQ 594.

Therefore, in view of the above, in view of the combined teachings of the prior art, one of ordinary skill in the art would have been motivated at the time the invention was made to employ a method for producing a protein for X-ray crystallographic analysis by synthesizing a protein using a cell-free extract, a nucleic acid coding for said protein and an amino acid for the substrate of said protein, wherein said amino acid comprises at least one amino acid comprising a heavy atom and a protein formulation thereof, absence of sufficient objective factual evidence or unexpected results to the contrary.

#### **CONCLUSION AND FUTURE CORRESPONDANCE**

4. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Abdel A. Mohamed whose telephone number is (703) 308-3966. The examiner can normally be reached on Monday through Friday from 7:30 a.m. to 5:00 p.m. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher S.F. Low can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 305-7401 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

*Christopher S.F. Low*  
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December 1, 2003